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Short-Term and Long-Term Outcomes of Interstitial Lung Disease in Polymyositis and Dermatomyositis

A Series of 107 Patients

I. Marie,[1] P. Y. Hatron,[2] S. Dominique,[3] P. Cherin,[4] L. Mouthon,[5] and J.-F. Menard[3]

Objective. **This study was undertaken to assess the characteristics and outcome of interstitial lung disease (ILD) in polymyositis/dermatomyositis (PM/DM) and to determine variables predictive of ILD deterioration in PM/DM.**

Methods. **Among 348 consecutive patients with PM/DM, 107 patients with ILD were identified by medical records search in 4 medical centers. All patients underwent pulmonary function tests (PFTs) and pulmonary high-resolution computed tomography (HRCT) scan.**

Results. **ILD onset preceded PM/DM clinical manifestations in 20 patients, was identified concurrently with PM/DM in 69 patients, and occurred after PM/DM onset in 18 patients. Patients with ILD could be divided into 3 groups according to their presenting lung manifestations: patients with acute lung disease (n = 20), patients with progressive-course lung signs (n = 55), and asymptomatic patients with abnormalities consistent with ILD evident on PFTs and HRCT scan (n = 32). We observed that 32.7% of the patients had resolution of pulmonary disorders, whereas 15.9% experienced ILD deterioration. Factors that predicted a poor ILD prognosis were older age, symptomatic ILD, lower values of vital capacity and diffusing capacity for carbon monoxide, a pattern of usual interstitial pneumonia on HRCT scan and lung biopsy, and steroid-refractory ILD. The mortality rate was higher in patients with ILD deterioration than in those without ILD deterioration (47.1% versus 3.3%).**

Conclusion. **Our findings indicate that ILD results in high morbidity in PM/DM. Our findings also suggest that more aggressive therapy may be required in PM/DM patients presenting with factors predictive of poor ILD outcome.**

Polymyositis (PM) and dermatomyositis (DM) are systemic inflammatory disorders that affect skeletal muscles and other organs, especially the lungs, either primarily or through complications of muscle weakness, resulting in interstitial lung disease (ILD), ventilatory insufficiency, and aspiration pneumonia (1–4). The prevalence of pulmonary involvement has been reported to be as high as 46% in PM/DM, and pulmonary disorders are still considered to be a common cause of morbidity in PM/DM (1–4). ILD may lead to life-threatening complications, i.e., ventilatory failure, secondary pulmonary arterial hypertension, or cor pulmonale (2,5–9). Previous studies of small series have shown that once pulmonary involvement was recognized in PM/DM, the 5-year mortality rate ranged from 0 to 55% (5,7,10). The early detection of ILD is, therefore, a high priority in PM/DM patients. The aims of this retrospective study were to assess the characteristics and outcome of ILD in patients with PM/DM and to determine factors that are predictive of ILD deterioration in PM/DM.

PATIENTS AND METHODS

Identification of the patients. This retrospective study began with a search of the institutional centers' medical record

[1]I. Marie, MD, PhD: Centre Hospitalier Universitaire Rouen, INSERM U 905, University of Rouen IFRMP, and Institute for Biochemical Research, Rouen, France; [2]P. Y. Hatron, MD: Centre Hospitalier Universitaire Lille, Lille, France; [3]S. Dominique, MD, J.-F. Menard, MD: Centre Hospitalier Universitaire Rouen, Rouen, France; [4]P. Cherin, MD, PhD: Hôpital Pitié-Salpêtrière, Paris, France; [5]L. Mouthon, MD, PhD: Université Paris Descartes and Hôpital Cochin, Paris, France.

Address correspondence to I. Marie, MD, PhD, Département de Médecine Interne, Centre Hospitalier Universitaire de Rouen, 1 Rue de Germont, 76031 Rouen Cedex, Rouen, France. E-mail: isabelle.marie@chu-rouen.fr.

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index, which provides access to the diagnoses of the centers' patients. The first electronic search involved use of the codes PM and DM to identify patients with a diagnosis of PM/DM seen from January 1995 to January 2010 in 4 academic centers (Lille, Cochin, Pitié-Salpêtrière, and Rouen). The diagnosis of PM/DM was based on the Bohan and Peter criteria (11,12), including symmetric muscle weakness, increased serum muscle enzymes, myopathic changes on electromyography, typical histologic findings on muscle biopsy, and characteristic dermatologic manifestations. During the study period, 348 consecutive patients were seen for evaluation of PM (n = 184) and DM (n = 164); none of these patients had other connective tissue disorders or myopathy.

A second search was conducted to isolate the subset of PM/DM patients who exhibited ILD. Among the 348 patients, 107 had ILD. One physician (IM) used a standard form to record the characteristics of patients from medical files. The data collected on the form included features and outcome data regarding the progression of ILD.

All patients underwent an initial evaluation of organ involvement, which resulted in the detection of systemic complications, including Raynaud's phenomenon, mechanic's hands, esophageal dysfunction, and joint impairment. The diagnosis of PM/DM-related esophageal involvement was based on the presence of clinical manifestations, i.e., dysphagia, gastroesophageal reflux into the pharynx and/or mouth, coughing while eating, or aphagia for solids and liquids. In the patients exhibiting esophageal symptoms, gastroscopy was performed to exclude mucosal involvement (esophagitis or ulcers) that might be responsible for dysphagia. Results of gastroscopy were normal in all patients. Patients were also examined for underlying malignancy.

Patients also underwent biochemical assessment. Erythrocyte sedimentation rate, C-reactive protein level, hemoglobin level, presence of leukocytosis, platelet count, and alanine aminotransferase, aspartate aminotransferase, and creatine kinase (CK) levels were determined. Autoantibody screening was performed for antinuclear antibodies and anti-SSA antibodies. The presence of anti–Jo-1, anti–PL-7, and anti–PL-12 antibodies was determined using immunodiffusion with subsequent confirmation by enzyme-linked immunosorbent assay. The presence of anti–Mi-2 antibody was assessed by immunodiffusion in patients with antinuclear antibody and a speckled pattern on immunofluorescence; positivity of this antibody was confirmed by immunodot. Screening for anti–PM-Scl antibody was performed by immunodiffusion in patients with antinuclear antibody and a speckled/nucleolar pattern on immunofluorescence; positivity of this antibody was confirmed by immunodot. The presence of anti–signal recognition particle (anti-SRP) antibody was assessed by immunodot as described previously (13).

Evaluation of ILD. ILD was systematically investigated initially by pulmonary function tests (PFTs) and pulmonary high-resolution computed tomography (HRCT) scan of the lungs; some patients also underwent lung biopsy.

Pulmonary symptoms. The clinical symptoms assessed were dyspnea, cough, and fever. Patients were subsequently classified into the following 3 groups according to ILD presentation: symptomatic acute onset of ILD (taking the form of antibiotic-resistant immunity-acquired pneumonia), symptomatic progressive onset of ILD, and asymptomatic disease with abnormalities consistent with ILD on PFTs and HRCT scan of the lungs.

Pulmonary function tests. The PFT parameters assessed were vital capacity (VC), forced vital capacity (FVC), and diffusing capacity for carbon monoxide (DLCO). VC and FVC were measured by spirometry (using a water-sealed spirometer); the DLCO was obtained by the single-breath method. Data are expressed as percentages of predicted values. The predicted values for each subject, based on sex, age, height, and weight, were obtained from standard tables (14). Lung function was considered abnormal when volumes were $<80\%$ of predicted values and when DLCO was $<70\%$ of the predicted value.

High-resolution computed tomography. HRCT of the lungs was performed to evaluate the presence of radiographic abnormalities consistent with ILD, i.e., parenchymal micronodules and nodules, irregular linear opacities, irregularity of the interfaces between peripheral pleura and aerated lung parenchyma, ground-glass opacities, honeycombing, and traction bronchiectases or bronchiolectases (15–17). Previous authors (7,18–20) have suggested that HRCT scan pattern may be correlated with pulmonary histologic findings. For instance, cryptogenic organizing pneumonia is mainly characterized by consolidation and linear opacities. Nonspecific interstitial pneumonia is principally characterized by ground-glass opacities and irregular linear opacities, usual interstitial pneumonia is mainly characterized by honeycombing and traction bronchiectases, and diffuse alveolar damage is usually defined by bilateral and extensive consolidation with airspace and ground-glass opacities. Our patients were, in fact, divided into 4 groups based on HRCT scan patterns indicative of cryptogenic organizing pneumonia, nonspecific interstitial pneumonia, usual interstitial pneumonia, and diffuse alveolar damage (7,18–21).

Lung biopsy. Forty-one patients underwent transbronchial or surgical lung biopsy at ILD diagnosis. Histologic analysis of lung biopsy specimens was performed to detect abnormalities consistent with ILD: cryptogenic organizing pneumonia, nonspecific interstitial pneumonia, usual interstitial pneumonia, or diffuse alveolar damage (21).

Outcome of ILD. The functional disease course for all patients with ILD was assessed for clinical manifestations, abnormal PFT findings, and HRCT abnormalities. The outcomes were categorized as resolution, improvement, or deterioration.

Resolution was defined as complete resolution of pulmonary symptoms associated with disappearance of radiographic signs of ILD and normalization of standard PFT values. Improvement was defined as when any of the former pulmonary alterations improved without returning to normal value. According to an international consensus statement of the American Thoracic Society on idiopathic pulmonary fibrosis (22), increases of $\geq 10\%$ in FVC and/or $\geq 15\%$ in DLCO were considered to be significant, and were used as determinants of improvement. Deterioration was defined as when any of the features of pulmonary condition worsened despite institution of therapy. According to an international consensus statement of the American Thoracic Society on idiopathic pulmonary fibrosis (22), decreases of $\geq 10\%$ in FVC and/or $\geq 15\%$ in DLCO were considered to be significant, and were used as determinants of deterioration. Finally, survival status and causes of death were based on hospital records.

Measurement of predictive factors. Factors predictive of ILD deterioration were assessed at ILD diagnosis. Patients were divided into 2 groups, those whose disease deteriorated due to ILD and those whose disease did not deteriorate due to ILD; clinical, biochemical, and paraclinical data were compared between these 2 groups of patients. For group comparisons involving binary data, we used either the chi-square test (for sample sizes of >5) or Fisher's exact test (for sample sizes of ≤5). Comparisons involving continuous data were made using the Mann-Whitney U test. *P* values less than 0.05 were considered significant.

RESULTS

Patient characteristics. Among 348 consecutive patients, 107 patients (30.7%) had ILD; 68 of the 184 patients with PM (37%) and 39 of the 164 patients with DM (23.8%) had ILD. PM/DM was considered definite in 74 patients who presented with at least 4 manifestations (of Bohan and Peter criteria) and probable in 33 patients; no patient had amyopathic DM. The patients with ILD consisted of 43 men and 64 women with a median age of 53 years at ILD diagnosis.

Characteristics of ILD. As shown in Table 1, ILD onset preceded initial PM/DM clinical manifestations in 20 patients, was concurrently identified in association with PM/DM in 69 patients, and occurred after PM/DM onset in 18 patients. At ILD diagnosis, pulmonary symptoms consisted of dyspnea (n = 73), cough (n = 38), and fever (n = 20). Patients were divided into the following 3 groups according to their presenting lung manifestations: patients with symptomatic acute onset of ILD (n = 20), patients with symptomatic progressive onset of ILD (n = 55), and asymptomatic patients exhibiting abnormalities consistent with ILD on PFTs and HRCT of the lungs (n = 32).

Antinuclear antibodies were reactive in 62 patients; 29 patients had anti-SSA antibody. Of the remaining antibodies tested, anti–Jo-1 was detected in 60 patients, anti–PL-7 in 2 patients, anti–PL-12 in 1 patient, and anti–PM-Scl in 7 patients. None of the patients had anti-SRP or anti–Mi-2 antibodies.

At ILD diagnosis, PFT results were consistent with ILD in all cases; the median values of PFT parameters were 73% for FVC, 74% for VC, and 57% for DLCO. At ILD diagnosis, PFT results indicated severe impairment, with DLCO values <45%, in 17.8% of patients (n = 19).

During the initial evaluation of ILD, HRCT scan of the lungs demonstrated the following abnormalities: parenchymal micronodules/nodules (in 30.8% of the patients; n = 33), linear opacities (83.2%; n = 89), irregularity of the interfaces (85%; n = 91), ground-glass opacities (77.6%; n = 83), honeycombing (25.2%; n = 27), consolidation (18.7%; n = 20), and traction bronchiectases/bronchiolectases (17.8%; n = 19). Based on pulmonary HRCT scan pattern, patients were divided into the following 3 groups: cryptogenic organizing pneumonia (n = 20), nonspecific interstitial pneumonia (n = 68), and usual interstitial pneumonia (n = 19).

Table 1. Characteristics of ILD in the 107 patients with PM/DM*

Presenting symptoms	
Symptomatic acute lung disease	18.7
Symptomatic progressive signs	51.4
Asymptomatic	29.9
Time of ILD onset	
Before PM/DM onset	18.7
Concomitant with PM/DM	64.5
After PM/DM onset	16.8
HRCT scan pattern	
Cryptogenic organizing pneumonia	18.7
Nonspecific interstitial pneumonia	63.6
Usual interstitial pneumonia	17.8
Lung biopsy†	
Cryptogenic organizing pneumonia	22
Nonspecific interstitial pneumonia	61
Usual interstitial pneumonia	17
ILD course	
Resolution	32.7
Improvement	51.4
Deterioration	15.9
Mortality	7.5

* Values are the percent of patients. ILD = interstitial lung disease; PM/DM = polymyositis/dermatomyositis; HRCT = high-resolution computed tomography.
† Performed in 41 patients.

Pulmonary biopsy specimens from 41 patients were subjected to histologic analysis, which showed damage consistent with cryptogenic organizing pneumonia in 9 patients, nonspecific interstitial pneumonia in 25 patients, and usual interstitial pneumonia in 7 patients. In all 41 patients, we found a correlation between HRCT scan pattern and histologic pulmonary damage.

Course of ILD. The median duration of ILD followup was 34 months (range 4–372 months).

ILD resolution. ILD resolved in 35 patients (32.7%), i.e., lung symptoms completely healed and PFT results returned to normal, associated with clearing of HRCT scan. Of these 35 patients, 16 had anti–Jo-1 antibodies, and 3 had anti–PM-Scl antibodies. Complete control of ILD was obtained with steroids alone in 24 patients, steroids and azathioprine in 5 patients, steroids and cyclophosphamide (6 pulses of 0.7 gm/m^2/month) in 5 patients, and steroids and cyclophosphamide (6 pulses of 0.7 gm/m^2/month) plus subsequent azathioprine in 1 patient.

Table 2. Comparison of the general and clinical characteristics of PM/DM patients with ILD deterioration and PM/DM patients without ILD deterioration*

	ILD deterioration (n = 17)	Absence of ILD deterioration (n = 90)
General characteristics		
Age, median (range) years	62 (36–83)	52 (18–74)†
% men/women	29.4/70.6	42.2/57.8
% with PM/% with DM	64.7/35.3	63.3/36.7
Clinical characteristics, %		
Myalgia	100	86.7
Muscle weakness	70.6	66.7
Raynaud's phenomenon	41.2	40.7
Mechanic's hands	29.4	21.1
Esophageal involvement	23.5	16.7
Joint manifestations	58.8	54.4
Malignancy	5.9	4.4

* PM/DM = polymyositis/dermatomyositis; ILD = interstitial lung disease.
† $P = 0.008$ versus the group with ILD deterioration.

ILD improvement. Fifty-five patients (51.4%) experienced either improvement (n = 37) or stabilization (n = 18) of ILD. Of these 55 patients, lung symptoms disappeared in 29, although these patients had persistent abnormalities on PFTs and HRCT scan. The remaining 26 patients had improvement in both pulmonary signs and the results of PFTs and/or HRCT. (HRCT results improved without reaching normal patterns.) Of the 55 patients, 35 had anti–Jo-1, 2 had anti–PL-12, and 4 had anti–PM-Scl antibodies. In this group, ILD was successfully treated with steroids alone in 26 patients, steroids and azathioprine in 15 patients, steroids and cyclophosphamide (6 pulses of 0.7 gm/m^2/month) in 6 patients, steroids and cyclophosphamide (6 pulses of 0.7 gm/m^2/month) plus subsequent azathioprine in 4 patients, and steroids and azathioprine plus subsequent mycophenolate mofetil (due to azathioprine inefficacy) in 4 patients.

ILD deterioration. In 17 patients (15.9%), pulmonary symptoms worsened despite therapy; ILD deterioration was also reflected on PFTs and HRCT scan. Of these 17 patients, 9 had anti–Jo-1 antibodies, and 1 had anti–PL-7 antibodies. Nine patients developed progressive respiratory failure with a median delay of 37.2 months, resulting in O_2 dependency and disability despite therapy. These 9 patients had acute onset of ILD, and 3 had anti–Jo-1 antibody. At last followup, 6 of these 9 patients had died of ILD complications. Treatments attempted (unsuccessfully) in the group of 17 patients with deterioration of lung disease included steroids alone in 6 patients; steroids and azathioprine in 1 patient, steroids and cyclophosphamide (6 pulses of 0.7 gm/m^2/month) in 2 patients, steroids and cyclophosphamide (6 pulses of 0.7 gm/m^2/month) with subsequent azathioprine in 6 patients, and steroids and azathioprine with subsequent mycophenolate mofetil (due to azathioprine inefficacy) in 1 patient. One patient was treated with steroids and cyclophosphamide (6 pulses of 0.7 gm/m^2/month) and subsequent azathioprine, followed by replacement of azathioprine with mycophenolate mofetil due to azathioprine inefficiency.

Mortality rate. Eight patients died; 87.5% of the deaths were due to lung complications. Death was due to pyogenic pneumonia as a complication of ILD, which

Table 3. Comparison of the pulmonary characteristics of PM/DM patients with ILD deterioration and PM/DM patients without ILD deterioration*

	ILD deterioration (n = 17)	Absence of ILD deterioration (n = 90)	*P*
Presenting pulmonary symptoms			
Fever	11.8	20	0.521
Dyspnea	94.1	63.3	0.01
Cough	64.7	30	0.01
Asymptomatic	5.9	34.4	0.01
Time of onset of ILD			
Before PM/DM onset	17.6	18.9	
Concomitant with PM/DM	58.8	65.6	0.721
After PM/DM onset	23.5	15.6	
Median PFT findings at ILD diagnosis, % predicted			
FVC	66	71	0.01
VC	70	75	0.01
DLCO	36	54	0.002
HRCT scan pattern			
Cryptogenic organizing pneumonia	11.8	20	0.521
Nonspecific interstitial pneumonia	52.9	65.6	0.411
Usual interstitial pneumonia	35.3	14.4	0.07
Lung biopsy†			
Cryptogenic organizing pneumonia	11.1	25	0.188
Nonspecific interstitial pneumonia	22.2	42.8	0.01
Usual interstitial pneumonia	66.7	32.2	0.0001
Mortality	47.1	3.3	0.000001

* Except where indicated otherwise, values are the percent of patients. PM/DM = polymyositis/dermatomyositis; ILD = interstitial lung disease; PFT = pulmonary function test; FVC = forced vital capacity; VC = vital capacity; DLCO = diffusing capacity for carbon monoxide; HRCT = high-resolution computed tomography.
† Performed in 41 patients.

Table 4. Biochemical findings in PM/DM patients with ILD deterioration and PM/DM patients without ILD deterioration*

	ILD deterioration (n = 17)	Absence of ILD deterioration (n = 90)
ESR, mm/hour	25.5 (8–75)	20 (1–222)
C-reactive protein, mg/liter	9 (3–212)	6 (1–104)
Hemoglobin, gm/dl	12.4 (10.3–14.1)	13.3 (9.2–17.2)
Total leukocyte count, $\times 10^9$/liter	9.2 (3.96–26.7)	7.85 (2.8–17)
Platelet count, $\times 10^9$/liter	257 (136–517)	279.5 (111–535)
Alanine aminotransferase, IU/liter	36 (15–151)	47 (2–390)
Aspartate aminotransferase, IU/liter	53 (18–266)	58 (6–490)
Creatine kinase, IU/liter	275 (35–4,601)	692 (24–25,231)
Antinuclear antibody positive, % of patients	47.1	60
Antisynthetase antibody positive, % of patients	52.9	60

* Except where indicated otherwise, values are the median (range). There were no significant differences between the group with interstitial lung disease (ILD) deterioration and the group without ILD deterioration. PM/DM = polymyositis/dermatomyositis; ESR = erythrocyte sedimentation rate.

occurred 4–26 months after ILD diagnosis, in 6 patients; respiratory failure related to ILD, which occurred 96 months after ILD onset, in 1 patient; and septicemia related to sigmoiditis at 24-month followup in 1 patient.

Factors associated with ILD deterioration. *Clinical data.* Patients with ILD deterioration were older than those without (median 62 years versus median 52 years). We found no statistically significant difference between patients with and those without ILD deterioration for sex, PM/DM subset, time of onset of ILD, fever, mechanic's hands, Raynaud's phenomenon, joint involvement, esophageal impairment, or cancer (P = 0.587) (Table 2). The presence of dyspnea and cough at ILD diagnosis could be considered factors predictive of deterioration (Table 3). Patients with symptomatic acute onset of ILD more commonly had deterioration of ILD compared with those presenting with the symptomatic progressive form (45% versus 17%; P = 0.01); fewer patients who were asymptomatic at ILD diagnosis had ILD deterioration than did patients who presented with symptoms (P = 0.01).

Patients who exhibited ILD deterioration had lower median values of FVC (P = 0.01), VC (P = 0.01), and DLco (P = 0.002) at initial ILD diagnosis. At last PFT followup, patients with ILD deterioration also presented with lower median values of FVC (47% versus 86%; P = 0.000001), VC (48% versus 85%; P = 0.000001), and DLco (21% versus 70%; P = 0.000001). With regard to HRCT scan findings, only the pattern of usual interstitial pneumonia was more frequent in the group of patients with ILD deterioration (P = 0.07). Histologic findings of cryptogenic organizing pneumonia (P = 0.188) and nonspecific interstitial pneumonia (P = 0.01) were more frequent in patients with resolution/improvement of ILD, whereas usual interstitial pneumonia damage was markedly correlated with ILD deterioration (P = 0.0001). In addition, steroid-refractory ILD was more frequently found in patients with ILD deterioration (75% versus 55%; P = 0.03). At last followup, patients with ILD deterioration still received higher median daily doses of prednisone (20 mg versus 7 mg; P = 0.000001).

Biochemical data. We found no correlation between deterioration of ILD and the median value of CK (P = 0.1) or between deterioration of ILD and the presence of antinuclear antibodies (P = 0.423), anti–Jo-1 antibodies (P = 0.752), or anti–PM-Scl antibodies (P = 0.428) (Table 4).

Mortality rate. The mortality rate was higher in patients with ILD deterioration than in those without (47.1% versus 3.3%; P = 0.000001).

DISCUSSION

ILD occurs in 26–64% of PM/DM patients (1,5–10,23). This retrospective study includes, to the best of our knowledge, the largest cohort of PM/DM patients with ILD; in this study, 107 consecutive PM/DM patients were included without any prior selection based on clinical presentation. Therefore, a selection bias based on the severity of the disease with overt or subclinical signs can be excluded.

The time of onset of ILD was variable in our patients, as previously described (5,7,9,10); in the present study, time of onset of ILD could not be considered a predictive factor of lung outcome. Moreover, we

observed that ILD often dominated the clinical course of PM/DM (in 70.1% of cases). The presenting clinical characteristics of ILD in PM/DM patients were similar to those observed in idiopathic forms of ILD (24). Many patients had symptomatic acute onset of ILD (18.7%), whereas other patients developed either progressive-onset ILD or an asymptomatic pattern of ILD. Acute onset of ILD has been suggested to be a factor predictive of poor prognosis in PM/DM (25,26). Interestingly, we found that PM/DM patients with acute onset of ILD more frequently developed deterioration of lung disease leading to O_2 dependency compared with other patients. Our findings do not confirm previous data suggesting that patients with acute and severe ILD more often present with amyopathic DM without anti–Jo-1 antibody; indeed, among the 9 patients in this study who developed acute onset of severe ILD requiring O_2 therapy, none had amyopathic DM, and one-third were positive for anti–Jo-1 antibody.

Our study confirms that PFTs and HRCT scan of the lungs are helpful tests for the diagnosis of ILD in PM/DM (5–8,10,21). A few authors have noted that reduced FVC and DLCO values were factors predictive of poor prognosis in PM/DM patients with ILD (27,28). In our large series of PM/DM patients, we observed a marked correlation between the onset of ILD deterioration and lower values of FVC/VC and DLCO at ILD diagnosis. Interestingly, we also found that the onset of ILD deterioration was associated with initial low values of DLCO ($<$45%) (in 42.1% of cases) and FVC ($\leq$65%) at the time of ILD diagnosis (in 41.2% of cases).

In our PM/DM patients, HRCT scan was useful to show ILD changes, with linear opacities, irregularity of the interfaces, and ground-glass opacities being the most common abnormalities. Another interesting finding of the present study was that HRCT scan of the lungs may provide data regarding ILD histologic pattern, as suggested previously (18–20). Our PM/DM patients presented more frequently with the nonspecific interstitial pneumonia pattern (63.6% of cases), followed by a cryptogenic organizing pneumonia pattern or usual interstitial pneumonia pattern. We further found that a pattern of usual interstitial pneumonia on HRCT scan was predictive of poor outcome in ILD.

Verschakelen (29) has recently underscored that it is possible to correctly diagnose ILD by HRCT scan when typical patterns of ILD are present, so that lung biopsy may be avoided in most cases. However, Verschakelen has mentioned that when HRCT signs are atypical, after multidisciplinary discussion of symptoms, a lung biopsy may be indicated in patients with ILD. In the present study, not all patients underwent transbronchial/open lung biopsy, because this test is an invasive method, and therefore it is not possible to conclude definitely that HRCT scan pattern is correlated with histologic data. Nevertheless, among our 41 PM/DM patients who underwent lung biopsy, we found a correlation between HRCT scan pattern and histologic damage in all cases; we have also demonstrated a marked correlation between histologic damage of usual interstitial pneumonia and the onset of ILD deterioration.

To date, 8 antisynthetase antibodies have been identified: anti–Jo-1, anti–PL-7, anti–PL-12, anti-OJ, anti-EJ, anti-KS, anti-Zo, and anti–tyrosyl–transfer RNA synthetase (6). Anti–Jo-1, anti-PL–7, and anti–PL-12 antibodies are the strongest markers for ILD; anti–Jo-1 antibody is the most common (6,27). The results of our study are consistent with these data; 58.9% of ILD patients had antisynthetase syndrome. A few previous studies have suggested that the clinical course of ILD patients with antisynthetase antibodies is better compared with that of other patients (9,30). The results of the present study do not confirm these data, since we did not find differences regarding the prognosis of ILD between patients with and without anti–Jo-1 antibody; interestingly, we found that anti–PM-Scl antibody was not predictive of ILD outcome in our patients. Finally, 2 new autoantibodies against melanoma differentiation–associated gene 5 and transcription intermediary factor 1γ have been found to be closely associated with ILD in DM patients (31); tests for these autoantibodies are not yet available in our centers.

To date, only a few investigators have assessed the long-term outcome of ILD in PM/DM patients (5,7,9,10). One study of 27 DM patients found pulmonary involvement to be the most frequent cause of death over a 10-year followup period (32). In the present study, 7.5% of our patients died, mainly of ILD complications (87.5% of cases). Moreover, our findings underscore that ILD is associated with a decrease in patients' functional status. In the present study, we found that only 32.7% of PM/DM patients with ILD had resolution of pulmonary disorders; in contrast, 39.1% of PM/DM patients with ILD exhibited a marked reduction of activities due to ILD course, and 9 ILD patients (8.4%) further developed respiratory failure resulting in O_2 dependency.

Therapy for ILD has not yet been clearly established in PM/DM patients. Corticosteroid therapy is considered the first-line therapy for PM/DM patients with ILD (6,8,10,21). Therapeutic response to steroids depends on pulmonary histologic findings rather than

clinical patterns; cryptogenic organizing pneumonia and nonspecific interstitial pneumonia are the forms considered to have the highest response to steroids (10,21,33,34). Our series has also shown an improved response to steroid therapy in patients with nonspecific interstitial pneumonia and cryptogenic organizing pneumonia compared with those with usual interstitial pneumonia, suggesting that early control of alveolitis may be required before it causes irreversible damage to the alveolar–capillary membrane. Interestingly, we further found that steroid-refractory ILD was a predictive factor of poor pulmonary outcome; patients with steroid-refractory ILD more often developed deterioration than did those without (75% versus 55%). Favorable outcome with immunosuppressive therapy in patients whose disease failed to respond to steroids alone has been reported previously.

Cyclophosphamide may improve the clinical outcome in these patients; intravenous pulse cyclophosphamide is most often used at a dose of 0.8 gm/m^2 (range 0.5–1 gm/m^2) monthly, although an oral regimen of 1.5–2 mg/kg/day might be preferred by some investigators (10,35–38). In a retrospective series, cyclophosphamide (0.3–0.8 gm/m^2 every 4 weeks for 6 cycles) was used in 17 PM/DM patients with ILD; at 7-month followup, dyspnea improved in 67% of the patients, and VC improved significantly in 47% of the cases (39). In a previous study, 10 patients with DM and acute histologically proven diffuse alveolar damage were given a combined therapy of prednisone, intravenous pulse cyclophosphamide (10–30 mg/kg every 3 weeks), and cyclosporine (2–3 mg per day); the authors observed an improvement in the 2-year survival rate for these patients (50%) (40).

Our series also suggests that cyclophosphamide is useful in PM/DM patients with ILD. In this study, 25 PM/DM patients with ILD were given intravenous pulse cyclophosphamide (0.5–0.8 gm/m^2 every 4 weeks for 3 cycles [n = 6] or 6 cycles [n = 19]). We observed that cyclophosphamide resulted in resolution or significant improvement of pulmonary status in 24% and 40% of cases, respectively. Five of these latter cyclophosphamide-treated patients, who had resolution/improvement of ILD, subsequently received azathioprine as maintenance therapy, which allowed stabilization of ILD in all cases. In the remaining patients (36%), ILD failed to respond to intravenous pulse cyclophosphamide; as pulmonary status continued to deteriorate gradually in these 9 latter patients, other treatments were started, including azathioprine (n = 6) and azathioprine and subsequent mycophenolate mofetil (n = 1), which also proved ineffective.

Only one case report of azathioprine as a helpful adjunctive maintenance therapy for the control of ILD has been described in PM/DM (41). In this instance, azathioprine was the most commonly used steroid-sparing agent in the treatment of PM/DM-related ILD. In the 38 azathioprine-treated patients with ILD in the present study, azathioprine was given either after the administration of intravenous pulse cyclophosphamide as maintenance therapy (n = 13) or in combination with prednisone (n = 25). In these latter 25 patients, azathioprine resulted in resolution or significant improvement of pulmonary status in 24% and 56% of cases, respectively. The 5 remaining patients (20%) failed to respond to azathioprine; because ILD worsened gradually, 4 of these 5 latter patients were given mycophenolate mofetil subsequently, resulting in significant improvement of ILD on PFT and HRCT scan.

An open trial of mycophenolate mofetil described in a previous report included 5 PM/DM patients with ILD who received mycophenolate mofetil at a dosage of 30 mg/kg/day; at the 18-month followup visit, findings of PFTs (FVC and DL$_{CO}$ values) were unchanged in most patients (42). In a small series, 3 PM/DM patients with ILD received steroids and mycophenolate mofetil, which resulted in resolution of ILD; however, because of the association of steroids with mycophenolate mofetil, it is difficult to conclude that mycophenolate mofetil is useful in PM/DM-associated ILD (43). In this study, 6 PM/DM patients with steroid-refractory ILD received mycophenolate mofetil (2–3 gm/day). The first patient was given mycophenolate mofetil as third-line therapy for ILD after failure of intravenous pulses of cyclophosphamide and azathioprine; in this patient with severe refractory ILD, mycophenolate mofetil also proved ineffective. Four additional patients had steroid/azathioprine-resistant ILD, and mycophenolate mofetil resulted in significant improvement in ILD, both clinically and on PFTs and HRCT scan in 3 of these 4 patients. The sixth patient with steroid-refractory ILD was given mycophenolate mofetil therapy, leading to significant improvement of pulmonary parameters. Taken together, our findings suggest that mycophenolate mofetil may be useful in PM/DM patients with ILD at early stages.

Finally, cyclosporine may be useful in steroid-resistant ILD related to PM/DM at a dose of 5–7.5 mg/kg/day (9,44–47). Nevertheless, cyclosporine therapy is difficult, as it requires monitoring during the first few months to ensure an optimal serum trough level (100–

200 mg/m) (48). Furthermore, cyclosporine is toxic to many organs, i.e., the kidneys, liver, and bone marrow. Consequently, renal findings should be closely monitored in PM/DM patients; when creatinine levels increase >30%, cyclosporine should be discontinued. In this study, no patient received cyclosporine as therapy for ILD.

In conclusion, our series highlights the fact that ILD results in increased morbidity and mortality in PM/DM. Our findings, in fact, indicate that PM/DM patients, with or without anti–Jo-1 antibody, should be routinely screened for ILD. Moreover, our study also suggests that the following parameters could be considered to be predictive of poor outcome in ILD: older age; symptomatic ILD; lower values of FVC, VC, and DLCO at ILD diagnosis; a pattern of usual interstitial pneumonia; and steroid-refractory ILD. The presence of these factors may suggest a need for more aggressive treatment of PM/DM patients with ILD.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Marie had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Marie, Hatron, Dominique, Cherin, Mouthon, Menard.

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Analysis and interpretation of data. Marie, Menard.

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